Gadoxetic acid enhanced MRI for diagnosis of focal nodular hyperplasia and hepatocellular adenoma: a systematic review.

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Target Audience: 1) Practicing radiologists who perform MR of the liver. 2) Scientists who work with liver specific contrast agents such as gadoxetic acid.

Purpose: The purpose of this study is to use systematic review to evaluate the diagnostic accuracy of hepatobiliary phase (HPB) gadoxetic-acid enhanced MRI (GA-MRI) of the liver for the diagnosis of focal nodular hyperplasia (FNH) vs. hepatocellular adenoma (HCA) in non-cirrhotic liver. ***Methods***: Multiple databases (Medline, Embase, CCTR, DARE, CSDR) with no language restrictions were searched up to Nov 5, 2014 for studies relevant to evaluation of FNH and HCA with GA-MRI. Inclusion criteria were applied to independently, in duplicate, as was data extraction. Data was extracted based on the principle that a 'true positive' was a diagnosis of FNH confirmed by the reference standard. Risk of bias of included studies was assessed using the QUADAS-2 tool. Between studies heterogeneity was not quantified, but a critical exploration for sources of heterogeneity was performed. Publication bias was not assessed since there is no accepted tool to do so in diagnostic accuracy studies. Sensitivity and specificity with 95%CI were plotted by forest plot; pooling was not done because only a small number of heterogeneous studies were included.

Results: Search identified 6 studies that met the inclusion criteria (309 patients, 164 HCA, 233 FNH). Forest plot of sensitivity and specificity is presented in figure 1. The sensitivity for diagnosis of FNH based on HPB phase was generally high ranging from 0.91-1.00 with the lower margin of the 95%CI reaching 0.77. The specificity was also generally high, but was considerably more variable. Specificity ranged from 0.87-1.00; the lower margin of the 95%CI reached 0.54. Assessment for risk of bias(figure 2) identified important sources of bias in: 1) patient selection (all were case-control studies which are known to over-estimate diagnostic accuracy. 2) Reference standard: only one study used molecular subtyping for diagnosis of HCA. 3) Use of MR as part of an imaging reference standard represents a potential important source of incorporation bias. No other convincing sources for heterogeneity were identified.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bieze 2012	27	1	1	23	0.96 [0.82, 1.00]	0.96 [0.79, 1.00]
Grazioli 2012	62	3	6	40	0.91 [0.82, 0.97]	0.93 [0.81, 0.99]
Greiser 2014	44	9	0	61	1.00 [0.92, 1.00]	0.87 [0.77, 0.94]
Mohajer 2012	34	0	0	6	1.00 [0.90, 1.00]	1.00 [0.54, 1.00]
Portiha 2011	23	0	1	8	0.96 [0.79, 1.00]	1.00 [0.63, 1.00]
Purysko 2012	32	0	3	12	0.91 [0.77, 0.98]	1.00 [0.74, 1.00]

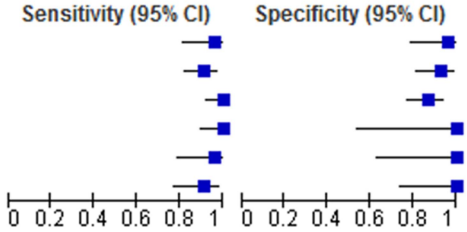

Figure 1: Forest plot of sensitivity and specificity for included studies.

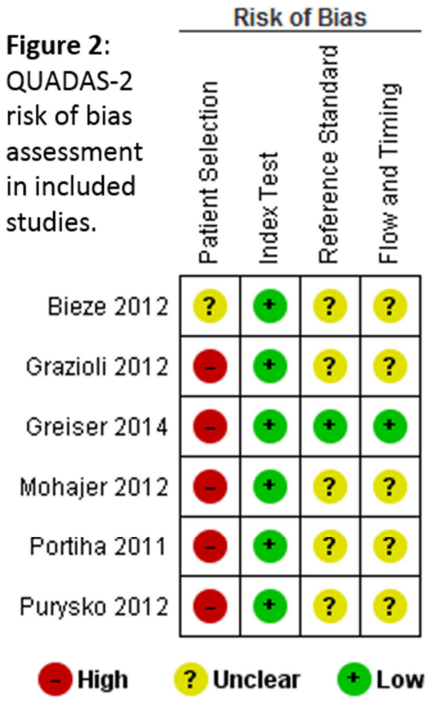

Figure 2: QUADAS-2 risk of bias assessment in included studies.

Discussion: This study identifies high diagnostic accuracy for hepatobiliary phase GA-MRI for diagnosis of FNH vs. HCA. However, all of the included studies had high risk of bias in multiple areas that indicates that these estimates may be too high. The most important weakness may be the lack of molecular subtyping of HCA. Without this, mis-classification of inflammatory HCA as FNH is possible; the only study to do so had the lowest specificity (Greiser *et al.*). In addition, 2 recent case series by Agarwal and Thomeer identify high rate uptake on HPB phase in inflammatory HCA; this is an important pitfall since this subtype comprises up to 50% of HCA and is an important potential source for false positives. Limitation of this study include small number of included studies and calculation of diagnostic accuracy on a per-lesion rather than per patient basis; this could lead to bias from clustering effect..

Conclusion: Although the reported diagnostic accuracy of HPB phase GA-MRI for diagnosis of HCA vs. FNH is high, the studies that support this conclusion may be considerably biased. Further research in the form of prospective cohort studies may improve our understanding of the limitations posed by our reliance on these studies.

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